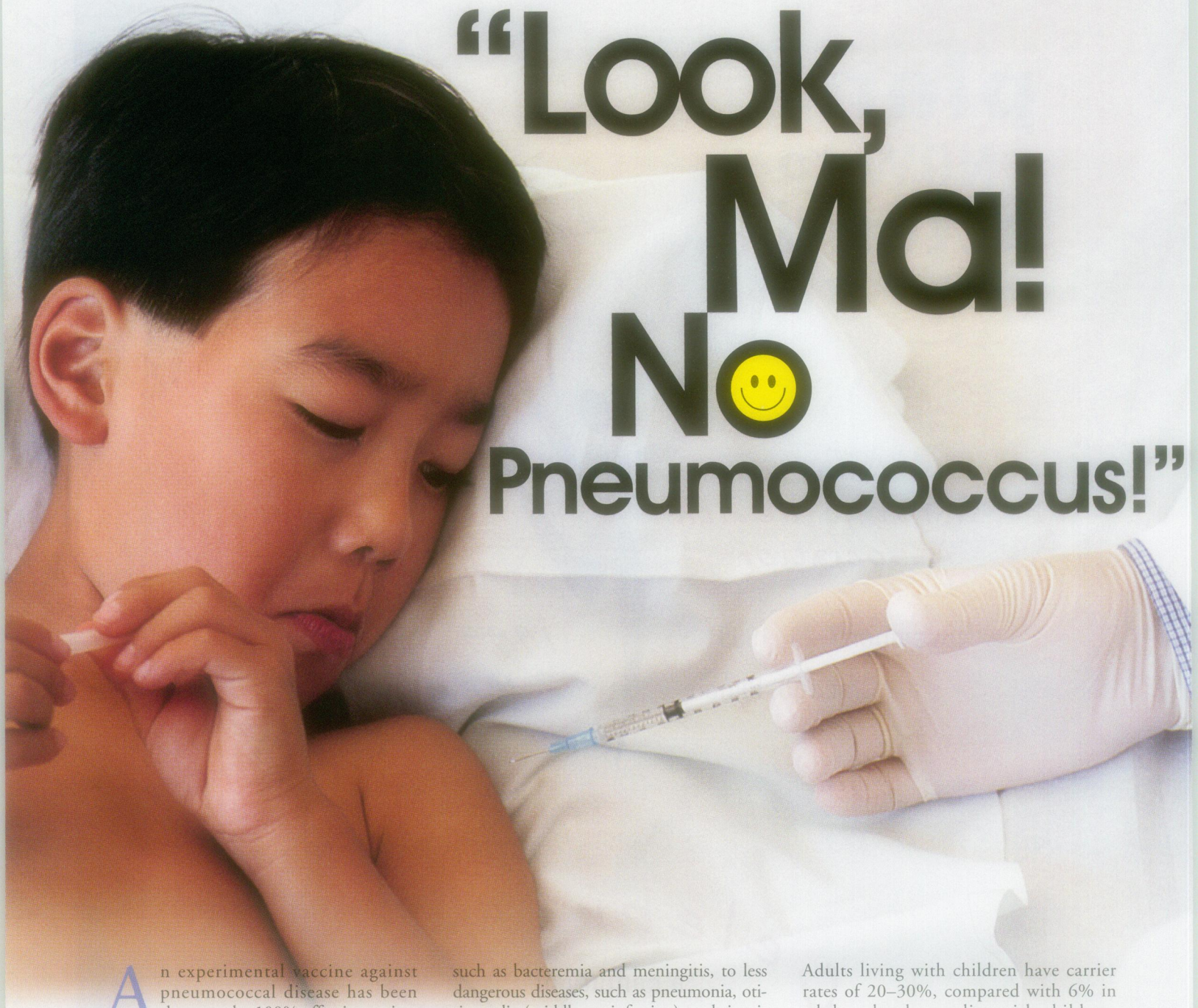
"Look, Ma! No Pneumococcus!"



An experimental vaccine against pneumococcal disease has been shown to be 100% effective against the two most deadly pneumococcal afflictions—bacterial meningitis (an infection of the brain and spinal cord) and bacteremia (a severe bloodstream infection). The vaccine, called PNCRM7, has been designated for the fast-track development program by the U.S. Food and Drug Administration (FDA). The fast-track program is designed to facilitate the development and expedite the review of new drugs and biologicals that are intended to treat serious or life-threatening conditions.

Pneumococcal disease is a group of illnesses caused by the bacterium *Streptococcus pneumoniae*, also known as pneumococcus. The illnesses range from severe infections, such as bacteremia and meningitis, to less dangerous diseases, such as pneumonia, otitis media (middle ear infection), and sinusitis. Each year in the United States, pneumococcus causes 3,000 cases of meningitis, 50,000 cases of bacteremia, 500,000 cases of pneumonia, and 7 million cases of otitis media, and is responsible for 40,000 deaths, according to the Centers for Disease Control and Prevention. Worldwide each year, pneumococcus causes 1.2 million deaths due to pneumonia, 39% of which are in children under the age of 5.

Children are both the major carriers and the major victims of pneumococcus, which spreads by person-to-person contact via respiratory secretions during sneezing or nose-blowing. Pneumococcal carrier rates run as high as 60% in young children. Adults living with children have carrier rates of 20–30%, compared with 6% in adults who do not live with children. Studies of children in Finland (published in the 15 March 1995 issue of the *Journal of the American Medical Association*) and Alaska (published in the February 1995 issue of the *Pediatric Infectious Disease Journal*) found that children under 2 years old who attend day care are at higher risk for pneumococcal infections—as much as 36-fold higher—than those who do not attend day care. Says Kevin Reilly, president of Wyeth Lederle Vaccines and Nutrition in Camp David, Pennsylvania, the company developing the vaccine, "Pneumococcal disease is a major threat to children all over the world, so it is particularly significant that the FDA has designated our vaccine for

fast-track review." The company plans to submit a product license application to the FDA by the middle of 1999.

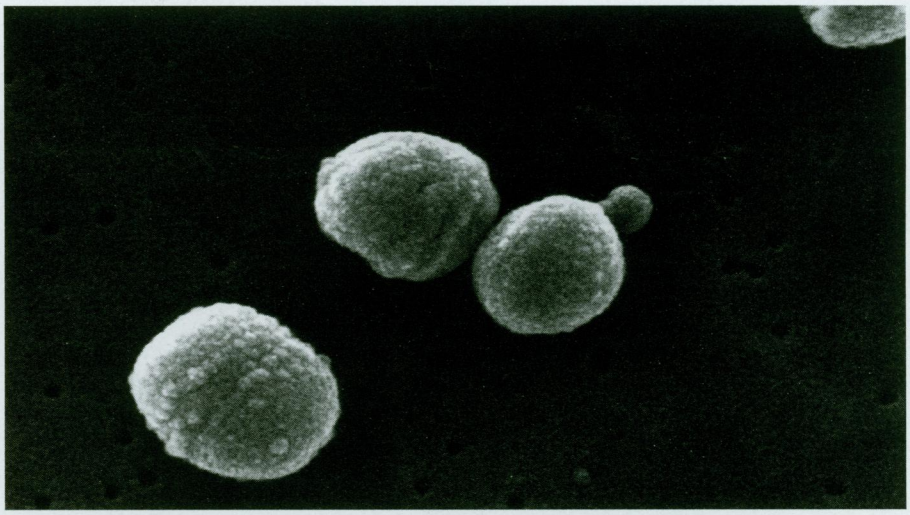
An Urgent Need

Pneumococcal illnesses have traditionally been treated with antibiotics. However, drug-resistant strains of pneumococcus have become increasingly common in the United States and other parts of the world, raising the risk of untreatable complications or death. Resistance to antibiotics such as penicillin, erythromycin, sulfa drugs, and cephalosporins has been reported. According to principal investigator Margaret Rennels, a professor of pediatrics at the University of Maryland School of Medicine in Baltimore, in some areas of the United States, as many as 50% of pneumococci are not sensitive to routine antibiotic treatments. This emerging antimicrobial resistance has "created an urgent need for a vaccine [that is] effective in young children," says pediatrician Henry Shinefield, codirector with Steven Black of the Kaiser Permanente Vaccine Study Center in Oakland, California.

In a three-year Phase III clinical trial involving 38,000 children, half of the infants received the pneumococcal vaccine by injection and half received an ineffective control vaccine at 23 Kaiser Permanente sites in northern California. Each child was dosed at 2, 4, and 6 months of age, and a booster dose was given at 12–15 months. By the end of the study, 22 cases of invasive pneumococcal disease (3 of meningitis and 19 of bacteremia) had occurred in the control group. None had occurred in the vaccine group—an efficacy rate of 100%. The only side effect was a mild fever lasting less than a day.

"For those of us who treat children with meningitis and bacteremia, this is an enormously exciting development," says Rennels, who conducted earlier safety trials of the vaccine. The results of the Phase III trial were presented 25 September 1998 at the "Interscience Conference on Antimicrobial Agents and Chemotherapy," held in San Diego, California, and were published in the April 1998 issue of *Pediatrics*.

The new vaccine contains capsular polysaccharides—the outer shell or coat of a microbe that triggers an immune response when injected—of 7 of the 80 known strains of *S. pneumoniae*. These seven strains cause up to 85% of bacteremia and meningitis and 65% of otitis media among young children. The vaccine is based on the same technology used by Wyeth Lederle to develop the *Haemophilus influenzae* type b conjugate vaccine, which was approved for use in infants in 1990. The first experimental pneumococcal vaccine contained five serotypes of *S. pneumoniae* (6B, 14, 18C, 19F, and 23F) conjugated to a carrier molecule called CRM197, and was proven safe and immunogenic in studies reported in February 1996 in the *Pediatric Infectious Disease Journal*. However, the addition of serotypes 4 and 9V increased the percentage of prevented infections from 65% to 85%. The current vaccine, which contains all seven serotypes conjugated to CRM197, improves protection without decreasing immunogenicity or increasing adverse reactions.



Janice Carr, CDC

Kiddie culprit. *Streptococcus pneumoniae* is the bacterium responsible for 7 million cases of otitis media, the most common bacterial infection in children, in the United States each year.

For Kids Only

The first vaccine for pneumococcal disease became available in 1944, but the advent of penicillin and other antibiotics led to an attitude that the need for vaccines would become obsolete. However, antibiotic resistance has rekindled interest in vaccine development. A pneumococcal vaccine for adults has been available for 15 years, but is ineffective in children, especially those younger than 2 years. The adult vaccine, generally given to people over 65 who have chronic debilitating illnesses, contains different serotypes than the vaccine being developed for children. "Adults get different pneumococcal diseases than children get," explains Shinefield.

It is believed that an effective pneumococcal vaccine could help reduce health care costs and curb the rise of antibiotic-resistant bacteria. On 4 May 1999, Shinefield and colleagues announced at the Pediatric Academy Society meeting in San Francisco, California, that the vaccine also reduced physician visits for otitis media by 9%. Half of all cases of acute otitis media, accounting for 12 million visits to pediatricians in the United States, are caused by pneumococcus. The total medical and societal costs of otitis media in children under the age of 5, including treatment expenses and lost wages of caregivers, exceed $5 billion each year. The newest finding, however, means that "one million children are not [going to be] coming to the doctor," says Shinefield. "That's one million fewer prescriptions a year that may be ineffective and contribute to antibiotic resistance."

Carol Potera

Suggested Reading

Rennels MB, Edwards KM, Keyserling HL, Reisinger KS, Hogerman DA, Madore DV, Chang I, Paradiso PR, Malinoski FJ, Kimura A. Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM197 in United States infants. Pediatrics 101(4):604–611 (1998).

Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Report 46(RR-8):1–24 (1997).